



# HHS Public Access

## Author manuscript

*Sex Transm Dis.* Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

*Sex Transm Dis.* 2019 June ; 46(6): 357–363. doi:10.1097/OLQ.0000000000000980.

## Proportion of Incident HIV Cases among Men Who Have Sex with Men Attributable to Gonorrhea and Chlamydia: A Modeling Analysis

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### Abstract

**Background**—Sexually transmitted infections (STIs) are associated with an increased risk of HIV acquisition and transmission. We estimated the proportion of HIV incidence among men who have sex with men attributable to infection with the two most common bacterial STIs, *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT).

**Methods**—We used a stochastic, agent-based model of a sexual network of MSM with co-circulating HIV, NG, and CT infections. Relative risk (RR) multipliers, specific to anatomic site of infection, modified the risk of HIV transmission and acquisition based on STI status. We estimated the effect of NG and CT on HIV incidence overall and on HIV acquisition and HIV transmission separately. Each scenario was simulated for ten years. The population attributable fraction (PAF) was determined for each combination of RRs by comparing the incidence in the final year of a scenario to a scenario in which the RRs associated with NG and CT were set to 1.0.

**Results**—Overall, 10.4% (IQR: 7.9,12.4) of HIV infections were attributable to NG/CT infection. Then in sensitivity analyses, the PAF for HIV transmission ranged from 3.1% (IQR: 0.5, 5.2) to 20.4% (IQR: 17.8, 22.5) and the PAF for HIV acquisition ranged from 2.0% (IQR: -0.7, 4.3) to 13.8% (IQR: 11.7, 16.0).

**Conclusions**—Despite challenges in estimating the causal impact of NG/CT on HIV risk, modeling is an alternative approach to quantifying plausible ranges of effects given uncertainty in the biological co-factors. Our estimates represent idealized public health interventions in which

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No conflicts to disclose.

STI could be maximally prevented, setting targets for real-world STI interventions that seek to reduce HIV incidence.

## Summary

Approximately 10% of incident HIV infections among MSM in the US are caused by prevalent gonorrhea or chlamydia infection.

## Introduction

Biological plausibility for a causal relationship between STI and HIV incidence is strong<sup>1–8</sup>, however, the population-level effect of common STIs, including *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG), on HIV incidence has been challenging to estimate. Further, most estimates have been obtained among heterosexual populations rather than men who have sex with men (MSM), with varying results from different studies.<sup>9,10</sup> One challenge has been to separate the effects of NG/CT on HIV acquisition and transmission risks. NG/CT are thought to increase the risk of HIV acquisition by damaging the genital or rectal epithelium or by increasing the availability of HIV target cells in the genital or rectal tracts.<sup>11</sup> Increased HIV transmission is thought to occur from increased viral shedding of HIV associated with prevalent NG/CT infection.<sup>11</sup>

Behavioral confounding may contribute to the observed association between prevalent STI and incident HIV. MSM with multiple sexual partners are more likely to be diagnosed with both HIV and STIs.<sup>12,13</sup> Because transmission for both STIs and HIV occur across the same network of sexual partnerships, it is difficult to separate the confounding factor of increased behavioral risk factors from the direct causal effects that STIs have on HIV risk.<sup>14</sup>

In this study, we used agent-based modeling to estimate the population attributable fraction (PAF) of NG/CT infection on HIV incidence among MSM in the United States. This approach allows the simulation of synthetic populations to directly observe the causal effect of NG/CT without confounding biases that are inherent in empirical observational study designs. Despite uncertainty from empirical studies regarding the effect of NG/CT on HIV risk, previous modeling studies have used fixed effects to model the relationship. By modeling the co-circulation of HIV, CT, and NG in this population we tested a range of plausible values for the effect of NG and CT infections on HIV acquisition and transmission that could set targets for the maximal effects on HIV incidence that could be achieved by a STI prevention intervention. We estimated the proportion of incident HIV infections attributable to NG and CT infections by comparing incidence in scenarios in which NG/CT contributed to HIV risk to a scenario in which NG/CT had no effect on HIV risk.

## Methods

In previous research, we developed a robust mathematical model for HIV/STI transmission dynamics for US MSM using the *EpiModel* software platform ([www.epimodel.org](http://www.epimodel.org)).<sup>15</sup> The EpiModel platform allows for simulating epidemics over dynamic sexual networks. The overall model structure, parameters, and outcomes are similar to Jenness et al.<sup>16</sup> Networks are comprised of dyads representing anal sex partnerships that may be one-time sexual

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encounters; casual, ongoing but shorter-duration partnerships; or main longer-duration partnerships. Predictors of partnership formation included age of partners, sexual role preferences, number of ongoing partnerships, and partner type. Behavioral components of the model were parameterized in part based on data from empirical sexual network studies conducted in Atlanta, Georgia.<sup>17,18</sup> Sexual activity within extant partnerships, including sexual position and condom use, was simulated on a weekly time step. Condom use varied based on partnership type (main, casual, and one-time), HIV diagnosis, and HIV status disclosure within partnerships. Specific parameter values and model structure are described in detail in the Appendix (Sections 2–3).

### HIV/STI Transmission and Disease Progression

Among partnerships that were discordant on HIV and/or STI status, transmission of HIV, NG, and CT occurred within simulated acts of anal intercourse. Probability of HIV transmission was modified by NG/CT infection (described in more detail below), viral load of the infected partner<sup>19</sup>, CCR5-delta 32 genetic allele status of the susceptible partner<sup>20</sup>, condom use<sup>21</sup>, sexual role<sup>22</sup>, and circumcision status of insertive partners.<sup>23</sup> Following infection, HIV disease progressed through acute, chronic, and AIDS stages dependent on current ART treatment status. HIV viral load was simulated as a continuous function of time since infection, disease stage, and current ART status. NG and CT infection remained active until diagnosis and antibiotic treatment (average treatment duration = 7 days) or natural clearance (average duration = 246 and 310 days, respectively).

### Effect of STI on HIV Transmission and Acquisition

Model parameters for relative risks (RRs) increased the per-act probability of transmission or acquisition of HIV conditional on prevalent NG/CT status. RRs were constant across the duration of NG/CT infection.

An overall PAF, combining the effects of STI on HIV acquisition and transmission, was calculated by comparing the scenario with RRs for which we have the strongest evidence to a scenario in which acquisition and transmission RRs were set to 1.0. The ‘strongest evidence’ RRs were the acquisition RRs from the base case scenario (rectal acquisition RR=1.97; urethral acquisition RR=1.48) and the transmission RRs were based on empirical evidence<sup>24</sup> (rectal and urethral transmission RR=1.3).

We also conducted sensitivity analyses in order to obtain a plausible range for the effect of NG/CT on HIV transmission and acquisition risk in isolation. NG/CT RRs affected HIV transmission or acquisition based on anatomical site of infection and sexual role. RRs for HIV transmission applied if (1) the HIV-infected partner had urethral NG or CT *and* was insertive during the sexual act, *or* (2) the HIV-infected partner had rectal NG or CT *and* was receptive during the sexual act. Similarly, RRs for HIV acquisition applied if (1) the HIV-uninfected partner had urethral NG or CT *and* was insertive during the sexual act, *or* (2) the HIV-uninfected partner had rectal NG or CT *and* was receptive during the sexual act.

We examined the effect of NG/CT on HIV incidence under a range of plausible RRs for HIV transmission and acquisition. Separate analyses were conducted to isolate the effects of HIV transmission versus HIV acquisition. To assess the potential impact of increased risk of HIV

acquisition due to NG/CT, acquisition RRs (Table 1) were varied while holding the transmission RR constant. In our previous applications, we only modeled the RR for each STI on HIV acquisition, with no increased risk for HIV transmission associated with prevalent STI.<sup>16</sup> To account for the effect of HIV transmission in the acquisition RR scenarios, a the ‘best evidence’ value RR of 1.3 was used for the effect of NG and CT infection on HIV transmission based on data obtained in an African cohort study.<sup>24</sup> No estimates of a transmission RR, as defined above, exist for MSM populations.

To assess the potential impact of increased risk of HIV transmission, transmission RRs were varied in separate models (Table 1), holding acquisition RR constant. Acquisition RRs were held constant at the levels that the base case of the model is calibrated to (rectal infection RR=1.97; urethral infection RR=1.48).

Estimates are not available for the effect of NG/CT co-infection. Thus, we conducted a sensitivity analysis evaluating two plausible biological mechanisms: 1) the highest RR from NG or CT prevailed; or 2) the co-infection RR was the product of the individual NG and CT RRs. We observed no clinically meaningful differences between these two scenarios. Results under the scenario that the highest RR prevailed are presented below; results under the multiplicative assumption are presented in the Appendix.

### **Model Scenarios**

Burn-in simulations were conducted to calibrate the model to observed HIV prevalence (15%<sup>25</sup>) and NG/CT incidence (3.5<sup>26,27</sup> and 5.6<sup>26</sup> incident infections/100 person-years, respectively). NC/CT incidence included both symptomatic and asymptomatic infections. Burn-in simulations were generated using the base-case HIV acquisition RRs, which were estimated for the acquisition RRs and fixed for the transmission RRs. Experimental scenarios for each combination of relative risks were simulated 256 times for 10 years each using the same starting burn-in simulation.

### **Measures**

Outcomes were estimated using the final year of the 10-year follow-up. The incidence rate per 100 PYAR was determined for each scenario in that interval. The PAF of NG/CT on HIV incidence was defined as:

$$PAF = \frac{(IR_i - IR_{ref})}{IR_i}$$

where  $IR_i$  is a scenario with specified RRs and  $IR_{ref}$  is the scenario with null RRs (i.e., RR = 1.0). To calculate the PAF for HIV acquisition attributable to NG/CT, the scenario in which all acquisition relative risks were set equal to 1.0 was the referent ( $IR_{ref}$ ).

The relative frequency of sexual acts resulting in HIV transmission were quantified based on the anatomical site of exposure and the prevalent NG/CT status of the newly-infected partner. As with the determination of the PAFs, the proportions reflect incident NG/CT that were role- and site-specific. First, transmission events were categorized based on whether a

rectal and/or urethral NG/CT infection was present. STIs were only counted if present in a role-specific site that could contribute to infection (e.g., prevalent urethral NG/CT in an insertive partner). Second, transmission events were categorized based on the NG/CT status of the newly HIV-infected partner.

The median and IQR of the PAF were determined for the final year of each comparison scenario using the null as the reference. All analyses were conducted in R 3.4.3. Analysis scripts and simulation data can be accessed at [https://github.com/EpiModel/sti\\_paf](https://github.com/EpiModel/sti_paf).

## Results

The estimated prevalence of HIV, NG, and CT over the last year of the burn-in model, which provided the starting point for each of the scenarios modeled, was 14.7% (IQR: 14.3,15.1), 1.3% (IQR: 0.9,1.5), and 3.7% (IQR: 3.3,4.1), respectively. Overall, considering the effects of NG/CT on HIV acquisition and transmission together, the PAF of NG/CT on HIV was 10.2% (IQR: 7.9,12.4) when comparing the ‘best estimate’ scenario to the null-effects scenario.

The results of the sensitivity analysis examining the effect of increased HIV transmission due to NG/CT are presented in Table 2. Holding the effect of NG/CT on HIV acquisition constant, the incidence of HIV increased as the RRs of NG/CT on HIV transmission increased. In the scenario assuming NG/CT did not affect HIV transmission, estimated incidence across simulations was 1.90 infections/100 PYAR (IQR: 1.86,1.94). The highest incidence was observed in the scenario with the highest RRs for NG/CT on HIV transmission (2.39/100 PYAR; IQR: 2.31,2.45). The PAF increased as the RRs of NG/CT on HIV transmission increased. Observed PAFs ranged from median values of 3.1% (IQR: 0.5,5.2) to 20.4% (IQR: 17.8,22.5).

The results of the sensitivity analysis examining the effect of increased HIV acquisition due to NG/CT are presented in Table 3. When NG/CT did not have an effect on HIV acquisition, the incidence rate was 1.83/100 PYAR (IQR: 1.78,1.87). The highest incidence rate was observed in the scenario with the highest RRs for NG/CT on HIV acquisition (2.12/100 PYAR; IQR: 2.07,2.17). In the base case scenario, with relative risks reflecting previous empirical and modeling work, the incidence rate was 1.96/100 PYAR (IQR: 1.91,2.01). The PAF of STI on HIV acquisition ranged from a low of 2.0% (IQR: -0.7,4.3) to a high of 13.8% (IQR: 11.7,16.0). In the base case scenario, the median PAF was 7.1% (IQR: 4.6,9.3).

Table 4 presents the proportions of HIV transmission events in which NG or CT infection were present at the site of sexual activity for one or both partners. Although these proportions do not indicate that NG/CT were causally related to the HIV transmission event, this table provides the distribution of NG/CT infection across these events. The proportion of transmission events in which NG or CT were present increased as the RRs for transmission and acquisition increased. Across the range of scenarios in which the relative risks for HIV transmission were varied, STI was present in one or both partners between 13.8%–28.6% of the time. When the relative risk for HIV acquisition was varied, STIs were present in one or both partners between 11.2%–21.0% of the time.

The proportion of HIV transmission events in which the newly HIV-infected partner had prevalent STI at the site of sexual activity is presented in Table 5. Overall, the proportion of HIV transmission events in which NG and CT were both present (i.e., dual-infection) never exceeded 1.0%. Across the range of transmission RRs, single- or dual-infection was present in 11.3% to 18.3% of newly-HIV-infected partners. Across the range of acquisition relative risks, single- or dual-infection was present in 7.5%–16.3% of newly-HIV-infected partners.

Prevalence of NG/CT was unaffected by changes in the HIV transmission and acquisition RRs. Across all scenarios, prevalence of any NG infection was 1% and prevalence of any CT infection was 3%.

## Discussion

We used agent-based modeling to estimate the potential population-level effects of highly prevalent bacterial STIs, NG and CT, on HIV incidence among MSM in the United States. We distinguished the effects of NG/CT on 1) HIV transmission from STI and HIV-infected men and 2) HIV acquisition by HIV-uninfected and STI-infected men. HIV incidence increased as the relative risks associated with HIV transmission and acquisition from an STI increased. Comparing a scenario in which our best estimates of the effect of NG/CT on HIV acquisition and transmission were in effect compared to a null condition in which there was no effect of NG/CT on HIV risk, we estimated that approximately 10% of HIV infections among MSM were attributable to NG/CT. This represents an estimate of the causal effect of NG/CT on HIV incidence, and therefore might represent the potential effect of a maximally efficient STI control intervention on HIV incidence in this population.

A difficult task in empirical studies<sup>28</sup> has been to isolate the effects of NG/CT on HIV transmission versus acquisition, as we did using a simulation-based approach. Disentangling these is critical from a public health perspective because it implies either a targeting of STI screening and treatment for HIV-infected versus HIV-uninfected MSM. For example, if prevalent STI has a stronger effect on HIV acquisition then this would indicate that, from a HIV prevention perspective, that screening of HIV-uninfected MSM would be most effective.

Few modeling studies of MSM have simulated the co-circulation of HIV and STIs among MSM, and ours may be the first that does so to explicitly investigate the population-level impact of prevalent NG/CT on HIV incidence in this population. Other modeling studies have assumed a fixed set of RR parameters, despite the major uncertainty of these parameter values.<sup>11</sup> There is little empirical evidence to inform these parameters, and yet, as our analysis shows, they have a substantial impact on the predicted HIV outcomes in modeling. Further, we were able to rigorously estimate the population-level effects of NG/CT by isolating the effects of these STIs based on sexual role and site of NG/CT infection. This type of data has proven to be very challenging to measure empirically because this requires identifying the sexual encounter that resulted in HIV infection, the sexual role(s) of each partner during that encounter, and the site-specific STI status of each partner. Sexual roles are critical for understanding the complex epidemiology of HIV/STI among MSM given the potential for bidirectional transmission in versatile partnerships. This concept of

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bidirectional transmission can facilitate the speed of transmission compared with fixed-role heterosexual partnerships.<sup>29</sup> Because NG and CT are typically site-specific rather than systemic infections, dynamic sexual roles remains a critical area for future epidemiological research.

Empirical data on the individual- and population-level effects of STI on HIV transmission and acquisition are limited. Trials and cohort studies conducted among heterosexuals in Africa have generally observed high prevalence of ulcerative STI.<sup>24,30,31</sup> Different classes of STIs present with symptoms (e.g., ulceration) that likely affect the transmission and acquisition of HIV differently. Further, sexual behaviors differ markedly between heterosexuals and MSM, and anal sex is more prevalent among the MSM population compared to heterosexuals.<sup>32</sup> Given the increased HIV transmission probabilities in rectal compared to vaginal sex<sup>33,34</sup>, it is likely that the effects of STI differ between heterosexual and MSM populations. Sexual role versatility<sup>29</sup> and the anatomic site of the STI might affect the dynamics of the interaction between STI and HIV.

These estimates have critical importance for both epidemiology science and public health efforts aimed at disease control. For the latter, our study contributes to the evidence base supporting interventions for STI screening and treatment as a mechanism towards prevention programs on HIV incidence. We estimate the PAF of STI on HIV acquisition to be between 2–14% and HIV transmission to be between 3–20%. Importantly, in our sensitivity analyses we held the effect of NG/CT on HIV transmission constant when examining RRs for HIV acquisition (and vice versa). Thus, these ranges might underestimate the true effect of NG/CT on HIV incidence if the effects we modeled underestimate the true RRs. Separately examining the effects of NG/CT on HIV acquisition and transmission can inform the potential impact of STI detection and treatment among HIV-uninfected and HIV-infected MSM on HIV incidence, respectively. Our overall estimate, comparing the scenario with acquisition and transmission RRs with the strongest evidence to a null scenario in which NG/CT do not affect HIV transmission or acquisition, indicates that approximately 10% of HIV incidence is due to NG/CT infection. This estimate corresponds to approximately 2,600 HIV infections that could be averted annually in the United States with the immediate and universal elimination of NG/CT through an idealized STI control intervention.<sup>35</sup> This sets the optimistic estimate sets the benchmark against which real-world interventions could be compared.

### Limitations.

First, we estimated the PAF of NG/CT on HIV incidence using experimental scenarios with different prevailing RRs for HIV transmission or acquisition that were all modeled using the same calibrated model. This resulted in increasing population-level HIV incidence as the RRs increased due to increasing HIV transmission. An alternative approach would be to generate separate burn-in models for each of the RR combinations with the same targeted equilibrium HIV prevalence. However, this method would also require adjustment of other behavioral or biological parameters (e.g., frequency of sex acts), in order to achieve the same HIV prevalence across different RR scenarios. The counterfactual scenarios presented in this analysis provide an estimate of the proportion of HIV incidence attributable to NG and CT

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when all other variables are held constant, analogous to an idealized STI control intervention. Second, the PAF values obtained in this analysis are inextricably linked to biological and behavioral factors. The prevalence of NG/CT, specifically the prevalence of NG/CT in HIV-discordant partnerships, has a direct impact on the PAF. Sexual networks with higher prevalence of NG/CT will have a greater proportion of HIV incidence attributable to NG/CT. Different levels of assortativeness, by degree or HIV/STI status, would also result in different PAF values, but we used a rigorous statistical analysis of empirical data on sexual network structure and behavior within partnerships to guide our base model. Our model was calibrated to national prevalence estimates of HIV. Nationally representative incidence rates for NG and CT are not available, so we estimated these rates from a cohort of MSM in Atlanta, Georgia.<sup>26,27</sup> Third, our model did not include other STIs that may impact HIV transmission, such as syphilis and herpes simplex virus, which also share the site-specific transmission characteristics of NG and CT. Finally, the model only estimates the effect of anal sex. Although oral sex is negligible in estimating HIV risk, it does play a role in STI transmission.<sup>36</sup> However, given our focus on the effect of NG and CT on HIV transmission and acquisition, the exclusion of oral sex from the model is unlikely to bias our results.

In conclusion, this study suggests that approximately 10% of HIV infections among MSM are attributable to NG/CT infection. In sensitivity analyses, we found that prevalent NG and CT contribute to between 2–14% of HIV acquisition and 3–20% of HIV transmissions among MSM. Public health strategies designed to detect and treat NG and CT among MSM in the United States might result in a meaningful reduction of HIV incidence among this high-risk population, although they must be part of a broader comprehensive strategy for HIV prevention that may also include consistent and correct condom use, choosing less risky sexual behaviors, routine testing for high-risk behaviors, drug treatment programs and using sterile equipment (for people who inject drugs), HIV pre-exposure prophylaxis<sup>37</sup> for uninfected MSM, and treatment as prevention<sup>38–40</sup> for HIV-infected MSM.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments and Funding

The authors would like to thank members of the scientific and public health advisory group of the Coalition for Applied Modeling for Prevention project for their input on this study, and specifically those members who reviewed a previous version of this manuscript: Thomas Bertrand, Mary Ann Chiasson, David Dowdy, Gregory Felzien, and Jonathon Poe. This work was supported by Centers for Disease Control and Prevention [grant: U38 PS004646], the National Institutes of Health [grants: R01 AI138783, R21 MH112449], and the Emory Center for AIDS Research [grant: P30 AI050409].

This work was supported by Centers for Disease Control and Prevention [grant: U38 PS004646], the National Institutes of Health [grants: R01 HD068395, R21 HD075662, R24 HD042828], and the Emory Center for AIDS Research [grant: P30 AI050409].

## References

1. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. *Lancet*. 1997;349(9069):1868–1873. [PubMed: 9217758]
2. Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9630):2109–2119. [PubMed: 18572080]
3. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010;362(5):427–439. [PubMed: 20089951]
4. Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. *Sex Transm Dis*. 2008;35(11):946–959. [PubMed: 18685546]
5. Moss GB, Overbaugh J, Welch M, et al. Human immunodeficiency virus DNA in urethral secretions in men: association with gonococcal urethritis and CD4 cell depletion. *J Infect Dis*. 1995;172(6):1469–1474. [PubMed: 7594704]
6. Rieg G, Butler DM, Smith DM, Daar ES. Seminal plasma HIV levels in men with asymptomatic sexually transmitted infections. *Int J STD AIDS*. 2010;21(3):207–208. [PubMed: 20215629]
7. Winter AJ, Taylor S, Workman J, et al. Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. *Sex Transm Infect*. 1999;75(4):261–263. [PubMed: 10615314]
8. Davies O, Costelloe S, Cross G, et al. Impact of rectal gonorrhoea and chlamydia on HIV viral load in the rectum: potential significance for onward transmission. *Int J STD AIDS*. 2017;28(10):1034–1037. [PubMed: 28081680]
9. Grosskurth H, Gray R, Hayes R, Mabey D, Wawer M. Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet*. 2000;355(9219):1981–1987. [PubMed: 10859054]
10. Barnabas RV, Wasserheit JN. Riddle of the Sphinx revisited: the role of STDs in HIV prevention. *Sex Transm Dis*. 2009;36(6):365–367. [PubMed: 19434009]
11. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. 1999;75(1):3–17. [PubMed: 10448335]
12. Koblin BA, Husnik MJ, Colfax G, et al. Risk factors for HIV infection among men who have sex with men. *AIDS*. 2006;20(5):731–739. [PubMed: 16514304]
13. Castillo R, Konda KA, Leon SR, et al. HIV and sexually transmitted infection incidence and associated risk factors among high-risk MSM and male-to-female transgender women in Lima, Peru. *J Acquir Immune Defic Syndr*. 2015;69(5):567–575. [PubMed: 25950207]
14. Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. *J Acquir Immune Defic Syndr*. 2010;53(4):537–543. [PubMed: 19935075]
15. Jenness SM, Goodreau SM, Morris M. EpiModel: An R package for mathematical modeling of infectious disease over networks. *Journal of statistical software*. 2018;84(8).
16. Jenness SM, Weiss KM, Goodreau SM, et al. Incidence of gonorrhea and chlamydia following human immunodeficiency virus preexposure prophylaxis among men who have sex with men: A modeling study. *Clin Infect Dis*. 2017;65(5):712–718. [PubMed: 28505240]
17. Sullivan PS, Rosenberg ES, Sanchez TH, et al. Explaining racial disparities in HIV incidence in black and white men who have sex with men in Atlanta, GA: a prospective observational cohort study. *Ann Epidemiol*. 2015;25(6):445–454. [PubMed: 25911980]
18. Hernandez-Romieu AC, Sullivan PS, Rothenberg R, et al. Heterogeneity of HIV prevalence among the sexual networks of black and white men who have sex with men in Atlanta: Illuminating a mechanism for increased HIV risk for young black men who have sex with men. *Sex Transm Dis*. 2015;42(9):505–512. [PubMed: 26267877]
19. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet*. 2008;372(9635):314–320. [PubMed: 18657710]

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20. Marmor M, Sheppard HW, Donnell D, Bozeman S, Celum C. Homozygous and heterozygous CCR5-[delta]32 genotypes are associated with resistance to HIV infection. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2001;27(5):472–481. [PubMed: 11511825]
  21. Smith DK, Herbst JH, Zhang X, Rose CE. Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States. J Acquir Immune Defic Syndr. 2015;68(3):337–344. [PubMed: 25469526]
  22. Goodreau SM, Carnegie NB, Vittinghoff E, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? PLoS One. 2012;7(11):e50522. [PubMed: 23209768]
  23. Wiysonge CS, Kongnyuy EJ, Shey M, et al. Male circumcision for prevention of homosexual acquisition of HIV in men. The Cochrane database of systematic reviews. 2011(6):CD007496. [PubMed: 21678366]
  24. Wall KM, Kilembe W, Vwalika B, et al. Risk of heterosexual HIV transmission attributable to sexually transmitted infections and non-specific genital inflammation in Zambian discordant couples, 1994–2012. Int J Epidemiol. 2017;46(5):1593–1606. [PubMed: 28402442]
  25. Rosenberg ES, Grey JA, Sanchez TH, Sullivan PS. Rates of prevalent HIV infection, prevalent diagnoses, and new diagnoses among men who have sex with men in US states, metropolitan statistical areas, and counties, 2012–2013. JMIR Public Health Surveill. 2016;2(1):e22. [PubMed: 27244769]
  26. Kelley CF, Vaughan AS, Luisi N, et al. The effect of high rates of bacterial sexually transmitted infections on HIV incidence in a cohort of black and white men who have sex with men in Atlanta, Georgia. AIDS Res Hum Retroviruses. 2015;31(6):587–592. [PubMed: 25719950]
  27. Stenger MR, Pathela P, Anschuetz G, et al. Increases in the rate of *Neisseria gonorrhoeae* among gay, bisexual and other men who have sex with men—Findings from the Sexually Transmitted Disease Surveillance Network 2010–2015. Sex Transm Dis. 2017;44(7):393–397. [PubMed: 28608788]
  28. Orroth KK, White RG, Korenromp EL, et al. Empirical observations underestimate the proportion of human immunodeficiency virus infections attributable to sexually transmitted diseases in the Mwanza and Rakai sexually transmitted disease treatment trials: Simulation results. Sex Transm Dis. 2006;33(9):536–544. [PubMed: 16778738]
  29. Goodreau SM, Golden MR. Biological and demographic causes of high HIV and sexually transmitted disease prevalence in men who have sex with men. Sex Transm Infect. 2007;83(6): 458–462. [PubMed: 17855487]
  30. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet. 1995;346(8974): 530–536. [PubMed: 7658778]

**Table 1.**

Relative risks (RRs) for HIV transmission and acquisition based on site of STI across modeled scenarios.

| Relative Risk of Transmission Analysis                             |                  |           |                 |          |
|--|------------------|-----------|-----------------|----------|
|  | Transmission RRs |           | Acquisition RRs |          |
|  | Gonorrhea        | Chlamydia | Rectal          | Urethral |
| Current base case scenario; Referent for HIV Transmission Analysis | 1.0              | 1.0       | 1.97            | 1.48     |
|  | 1.0              | 2.0       | 1.97            | 1.48     |
|  | 1.0              | 3.0       | 1.97            | 1.48     |
|  | 2.0              | 1.0       | 1.97            | 1.48     |
|  | 2.0              | 2.0       | 1.97            | 1.48     |
|  | 2.0              | 3.0       | 1.97            | 1.48     |
|  | 3.0              | 1.0       | 1.97            | 1.48     |
|  | 3.0              | 2.0       | 1.97            | 1.48     |
|  | 3.0              | 3.0       | 1.97            | 1.48     |
|  |                  |           |                 |          |
| Relative Risk of Acquisition Analysis                              |                  |           |                 |          |
|  | Transmission RRs |           | Acquisition RRs |          |
|  | Gonorrhea        | Chlamydia | Rectal          | Urethral |
| Base case acquisition RRs  | 1.3              | 1.3       | 1.97            | 1.48     |
|  | 1.3              | 1.3       | 1.0             | 1.0      |
|  | 1.3              | 1.3       | 1.0             | 2.0      |
|  | 1.3              | 1.3       | 2.0             | 1.0      |
|  | 1.3              | 1.3       | 2.0             | 2.0      |
|  | 1.3              | 1.3       | 2.0             | 3.0      |
|  | 1.3              | 1.3       | 3.0             | 1.0      |
|  | 1.3              | 1.3       | 3.0             | 2.0      |
|  | 1.3              | 1.3       | 3.0             | 3.0      |
|  |                  |           |                 |          |

**Table 2.**

The effect of relative risk for HIV transmission on HIV incidence.

| Relative Risk of HIV Transmission by STI |           | HIV Incidence Rate                   | Population Attributable Fraction |
|--|-----------|--------------------------------------|----------------------------------|
| Gonorrhea                                | Chlamydia | Rate per 100 PYAR <sup>1</sup> (IQR) | % (IQR)                          |
| 1.0                                      | 1.0       | 1.90 (1.86, 1.94)                    | Ref <sup>2</sup>                 |
| 1.0                                      | 2.0       | 2.02 (1.97, 2.06)                    | 5.9 (3.4, 7.9)                   |
| 1.0                                      | 3.0       | 2.13 (2.08, 2.18)                    | 10.7 (8.6, 12.9)                 |
| 2.0                                      | 1.0       | 1.96 (1.91, 2.00)                    | 3.1 (0.5, 5.2)                   |
| 2.0                                      | 2.0       | 2.11 (2.06, 2.16)                    | 10.1 (8.0, 12.2)                 |
| 2.0                                      | 3.0       | 2.27 (2.21, 2.33)                    | 16.2 (14.1, 18.5)                |
| 3.0                                      | 1.0       | 2.01 (1.96, 2.05)                    | 5.6 (3.0, 7.5)                   |
| 3.0                                      | 2.0       | 2.18 (2.11, 2.24)                    | 12.8 (10.2, 15.1)                |
| 3.0                                      | 3.0       | 2.39 (2.31, 2.45)                    | 20.4 (17.8, 22.5)                |

<sup>1</sup>Person years at risk;

<sup>2</sup>Base case scenario; HIV acquisition relative risks were held constant at base case values, rectal RR = 1.97, urethral RR = 1.48.

**Table 3.**

The effect of relative risk for HIV acquisition on HIV incidence

| Relative Risk of HIV Acquisition by STI Anatomic Site |          | HIV Incidence Rate       | Population Attributable Fraction |
|---|----------|--------------------------|----------------------------------|
| Rectal  | Urethral | Rate per 100 PYAR* (IQR) | % (IQR)                          |
| 1.97  | 1.48     | 1.96 (1.91, 2.01)        | 7.1 (4.6, 9.3)                   |
| 1.0   | 1.0      | 1.83 (1.78, 1.87)        | Ref                              |
| 1.0   | 2.0      | 1.86 (1.81, 1.91)        | 2.0 (-0.7, 4.3)                  |
| 1.0   | 3.0      | 1.89 (1.84, 1.93)        | 3.2 (0.8, 5.3)                   |
| 2.0   | 1.0      | 1.93 (1.89, 1.98)        | 5.6 (3.6, 7.8)                   |
| 2.0   | 2.0      | 1.98 (1.94, 2.02)        | 7.7 (5.9, 9.8)                   |
| 2.0   | 3.0      | 2.00 (1.95, 2.04)        | 8.6 (6.4, 10.7)                  |
| 3.0   | 1.0      | 2.02 (1.97, 2.07)        | 9.6 (7.4, 11.9)                  |
| 3.0   | 2.0      | 2.07 (2.03, 2.12)        | 12.0 (10.0, 13.9)                |
| 3.0   | 3.0      | 2.12 (2.07, 2.17)        | 13.8 (11.7, 16.0)                |

\* Person years at risk; HIV transmission relative risks were held constant at rectal RR = 1.3 and urethral RR = 1.3.

**Table 4.**

Proportion of transmission events in which site- and role-specific rectal and/or urethral STI were present.

|  |           | Anatomic Sites of Sexual Activity with Prevalent STI |                |                |                   |
|--|-----------|--|----------------|----------------|-------------------|
| Relative Risk of HIV Transmission by STI |           | Median (IQR) Proportion of Transmission Events       |                |                |                   |
| Gonorrhea                                | Chlamydia | Rectal and Urethral                                  | Rectal Only    | Urethral Only  | Neither           |
| 1.0                                      | 1.0       | 6.6 (6.3, 7.0)                                       | 5.4 (5.1, 5.9) | 2.7 (2.4, 3.0) | 85.3 (84.1, 86.2) |
| 1.0                                      | 2.0       | 8.7 (8.4, 9.2)                                       | 5.5 (5.1, 5.8) | 4.0 (3.6, 4.2) | 81.9 (80.8, 83.0) |
| 1.0                                      | 3.0       | 10.2 (9.8, 10.5)                                     | 5.5 (5.2, 5.9) | 4.9 (4.6, 5.2) | 79.3 (78.4, 80.4) |
| 2.0                                      | 1.0       | 7.6 (7.1, 7.9)                                       | 5.6 (5.2, 6.0) | 3.1 (2.8, 3.3) | 83.7 (82.8, 84.8) |
| 2.0                                      | 2.0       | 10.1 (9.8, 10.6)                                     | 6.2 (5.8, 6.5) | 4.5 (4.1, 4.8) | 79.2 (78.1, 80.3) |
| 2.0                                      | 3.0       | 12.0 (11.7, 12.3)                                    | 6.8 (6.5, 7.2) | 5.7 (5.4, 6.0) | 75.4 (74.5, 76.4) |
| 3.0                                      | 1.0       | 8.5 (8.1, 8.9)                                       | 6.1 (5.7, 6.2) | 3.4 (3.1, 3.8) | 82.0 (81.1, 83.0) |
| 3.0                                      | 2.0       | 11.1 (10.7, 11.4)                                    | 6.8 (6.5, 7.2) | 5.0 (4.7, 5.3) | 77.1 (76.1, 78.1) |
| 3.0                                      | 3.0       | 13.0 (12.8, 13.3)                                    | 7.9 (7.7, 8.2) | 6.6 (6.4, 7.0) | 72.4 (71.4, 73.2) |

  

|   |          | Anatomic Sites of Sexual Activity with Prevalent STI |                |                |                   |
|---|----------|--|----------------|----------------|-------------------|
| Relative Risk of HIV Acquisition by STI Anatomic Site |          | Median (IQR) Proportion of Transmission Events       |                |                |                   |
| Rectal  | Urethral | Rectal and Urethral                                  | Rectal Only    | Urethral Only  | Neither           |
| 1.97  | 1.48     | 7.4 (7.1, 7.7)                                       | 5.4 (5.0, 5.7) | 3.0 (2.8, 3.3) | 84.2 (83.3, 85.1) |
| 1.0   | 1.0      | 4.7 (4.3, 5.0)                                       | 3.6 (3.2, 3.9) | 2.9 (2.5, 3.2) | 88.8 (87.9, 89.9) |
| 1.0   | 2.0      | 5.2 (4.8, 5.5)                                       | 4.0 (3.6, 4.2) | 3.3 (2.9, 3.6) | 87.6 (86.6, 88.6) |
| 1.0   | 3.0      | 5.9 (5.6, 6.2)                                       | 4.5 (4.1, 4.8) | 3.7 (3.3, 4.0) | 85.9 (85, 86.9)   |
| 2.0   | 1.0      | 6.8 (6.6, 7.2)                                       | 5.0 (4.6, 5.3) | 2.8 (2.5, 3.1) | 85.4 (84.3, 86.3) |
| 2.0   | 2.0      | 7.8 (7.5, 8.1)                                       | 5.6 (5.3, 5.9) | 3.3 (3.0, 3.6) | 83.3 (82.4, 84.3) |
| 2.0   | 3.0      | 8.3 (7.9, 8.6)                                       | 6.0 (5.6, 6.3) | 3.6 (3.3, 3.8) | 82.2 (81.2, 83.2) |
| 3.0   | 1.0      | 8.5 (8.2, 8.8)                                       | 6.1 (5.8, 6.4) | 2.8 (2.6, 3.1) | 82.6 (81.6, 83.3) |
| 3.0   | 2.0      | 9.4 (9.1, 9.8)                                       | 6.7 (6.3, 7.0) | 3.2 (2.9, 3.4) | 80.6 (79.8, 81.7) |
| 3.0   | 3.0      | 10.2 (9.7, 10.5)                                     | 7.3 (7.1, 7.5) | 3.6 (3.3, 3.8) | 79.0 (78.2, 79.9) |

**Table 5.**

Proportion of transmission events in which the newly HIV-infected partner had site- and role-specific gonorrhea and/or chlamydia.

|  |           | STI Status of Newly HIV-Infected Partner       |                |                   |                   |
|--|-----------|--|----------------|-------------------|-------------------|
| Relative Risk of HIV Transmission by STI |           | Median (IQR) Proportion of Transmission Events |                |                   |                   |
| Gonorrhea                                | Chlamydia | Gonorrhea and Chlamydia                        | Gonorrhea Only | Chlamydia Only    | Neither           |
| 1.0                                      | 1.0       | 0.3 (0.2, 0.6)                                 | 3.0 (2.7, 3.3) | 7.9 (7.5, 8.3)    | 88.7 (87.8, 89.5) |
| 1.0                                      | 2.0       | 0.4 (0.3, 0.6)                                 | 3.1 (2.8, 3.4) | 9.8 (9.3, 10.2)   | 86.7 (85.7, 87.6) |
| 1.0                                      | 3.0       | 0.5 (0.4, 0.7)                                 | 3.3 (3.0, 3.6) | 10.9 (10.5, 11.3) | 85.2 (84.4, 86.1) |
| 2.0                                      | 1.0       | 0.4 (0.3, 0.7)                                 | 4.0 (3.7, 4.3) | 7.6 (7.2, 8.0)    | 87.9 (87.0, 88.7) |
| 2.0                                      | 2.0       | 0.6 (0.6, 0.9)                                 | 4.5 (4.1, 4.8) | 9.6 (9.3, 10.0)   | 85.3 (84.3, 86.1) |
| 2.0                                      | 3.0       | 0.9 (0.7, 1.1)                                 | 4.8 (4.5, 5.1) | 11.2 (10.8, 11.6) | 83.1 (82.3, 84.0) |
| 3.0                                      | 1.0       | 0.6 (0.3, 0.7)                                 | 4.9 (4.4, 5.1) | 7.8 (7.6, 8.3)    | 86.7 (85.8, 87.7) |
| 3.0                                      | 2.0       | 0.8 (0.6, 1.0)                                 | 5.3 (5.0, 5.7) | 9.8 (9.5, 10.1)   | 84.0 (83.2, 84.9) |
| 3.0                                      | 3.0       | 1.0 (0.8, 1.2)                                 | 5.9 (5.6, 6.3) | 11.4 (11.0, 11.7) | 81.7 (80.8, 82.7) |

  

|   |          | STI Status of Newly HIV-Infected Partner       |                |                   |                   |
|---|----------|--|----------------|-------------------|-------------------|
| Relative Risk of HIV Acquisition by STI Anatomic Site |          | Median (IQR) Proportion of Transmission Events |                |                   |                   |
| Rectal  | Urethral | Gonorrhea and Chlamydia                        | Gonorrhea Only | Chlamydia Only    | Neither           |
| 1.97  | 1.48     | 0.4 (0.2, 0.5)                                 | 3.4 (3.0, 3.7) | 8.0 (7.7, 8.3)    | 88.2 (87.4, 89.1) |
| 1.0   | 1.0      | 0.2 (0.1, 0.3)                                 | 2.2 (1.9, 2.4) | 5.1 (4.7, 5.5)    | 92.5 (91.8, 93.3) |
| 1.0   | 2.0      | 0.2 (0.1, 0.3)                                 | 2.2 (2.0, 2.5) | 5.8 (5.4, 6.2)    | 91.7 (91, 92.5)   |
| 1.0   | 3.0      | 0.4 (0.2, 0.5)                                 | 2.7 (2.3, 2.9) | 6.4 (6.2, 6.9)    | 90.5 (89.7, 91.3) |
| 2.0   | 1.0      | 0.3 (0.2, 0.4)                                 | 3.1 (2.7, 3.3) | 7.7 (7.3, 8.0)    | 88.9 (88.3, 89.8) |
| 2.0   | 2.0      | 0.4 (0.3, 0.6)                                 | 3.5 (3.1, 3.8) | 8.6 (8.2, 8.9)    | 87.5 (86.7, 88.4) |
| 2.0   | 3.0      | 0.4 (0.3, 0.6)                                 | 3.6 (3.3, 3.9) | 9.1 (8.7, 9.5)    | 86.8 (86, 87.7)   |
| 3.0   | 1.0      | 0.4 (0.3, 0.5)                                 | 3.7 (3.4, 4.1) | 9.6 (9.2, 9.9)    | 86.3 (85.5, 87)   |
| 3.0   | 2.0      | 0.5 (0.3, 0.6)                                 | 4.2 (3.9, 4.4) | 10.4 (10.1, 10.9) | 84.9 (84.1, 85.7) |
| 3.0   | 3.0      | 0.5 (0.4, 0.7)                                 | 4.5 (4.2, 4.8) | 11.3 (10.8, 11.7) | 83.7 (82.8, 84.5) |